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(71) Applicant *(for all designated States except US)*: MERCK SHARP & DOHME LIMITED [GB/GB]; Hertfort Road, Hoddesdon, Hertfordshire EN11 9BU (GB).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: BOYCE, Susan [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).

(74) Agent: HORGAN, James; Merck & Co., Inc., European Patent Dept., Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).

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(54) Title: COMBINATION OF A SELECTIVE NMDA NR2B ANTAGONIST AND A COX-2 INHIBITOR

(57) Abstract

The present invention provides a combination of a selective NMDA NR2B antagonist and a COX-2 inhibitor for the treatment or prevention of pain or nociception.

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# COMBINATION OF A SELECTIVE NMDA NR2B ANTAGONIST AND A COX-2 INHIBITOR

This invention relates to the treatment or prevention of pain or nociception by the administration of a combination of a selective NMDA NR2B antagonist and a COX-2 inhibitor.

Pain has been defined as the sensory experience perceived by nerve tissue distinct from sensations of touch, pressure, heat and cold. It is often described by sufferers by such terms as bright, dull, aching, pricking, cutting, burning, etc. This range of sensations, as well as the variation in perception of pain by different individuals, renders a precise definition of pain near impossible. Pain as suffering, however, is generally considered to include both the original sensation and the reaction to that sensation. Where pain is "caused" by the stimulation of nociceptive receptors and transmitted over intact neural pathways, this is termed nociceptive pain. Alternatively, pain may be caused by damage to neural structures, often manifesting itself as neural supersensitivity, and is classed as neuropathic pain.

The level of stimulation at which pain is perceived is referred to as the "pain threshold". Where the pain threshold is raised, for instance, by the administration of an analgesic drug, a greater intensity or more prolonged stimulus is required before pain is experienced. Analgesics are a class of pharmaceutical agent which, following administration to a patient in need of such treatment, relieve pain without loss of consciousness. This is in contrast to other pain-relieving drugs, for example, general anaesthetics which obtund pain by producing a hiatus in consciousness, or local anaesthetics which block transmission in peripheral nerve fibres thereby preventing pain.

NMDA (N-methyl-D-aspartate)-type glutamate receptors are believed to play a pivotal role in the transmission of excitatory signals from primary sensory neurones to the brain through the spinal cord

(A. H. Dickenson (1990) Trends Pharmacol. Sci., 11, 307-309). NMDA receptors mediate $Ca^{2+}$ influx into neurones, and its receptor-gated channel activity is blocked by $Mg^{2+}$ in a voltage-dependant manner. Subunits of the NMDA receptors are classified into two gene families, i.e., NR1 and NR2. A variety of compounds have been designed as antagonists targeting these subunits of the NMDA receptor for the treatment of neurodegenerative disorders, as well as acute and/or chronic pain and hyperalgesia. The NR2B subunit is predominantly expressed in the hippocampus (Ishii *et al.*, (1993), J. Biol. Chem. 268, 2836-2843).

NMDA antagonists such as ketamine, dextromethorphan and CPP are known to have analgesic properties in man. However, these agents also induce unacceptable side-effects including hallucinations, dysphoria and cognitive and motor disturbances (see Kristensen *et al.*, 1992, Pain, 51, 249ff; Price *et al.*, 1994, Pain, 59, 165ff and Max *et al.*, Clin. Neuropharmacol., 118, 360ff). In preclinical studies, dextromethorphan has been reported to potentiate the antinociceptive effects of NSAIDS and morphine (Price *et al.*,1996, Pain, 68, 119-127; Mao *et al.*, 1996, Pain, 67, 361-368). However, since dextromethorphan can induce adverse effects at analgesic doses in man, it is not clear from these studies whether such combinations would still be dogged with unwanted side-effects.

One selective NMDA NR2B antagonist CP-101,606 is known to possess anti-nociceptive activity, see Taniguchi *et al.*, B. J. Pharmacol., 1997, 122, 809-812. Potent analgesic activity of this compound was shown in rat hyperalgesic and nociceptive tests at doses showing no behavioural abnormality.

There is, however, no general teaching in the art that all selective NMDA NR2B antagonists are useful as analgesics, nor that they have improved motor side-effect profile compared to NMDA/glycine antagonists. Evidence for this is, for the first time, provided herein.

Furthermore there is no suggestion in the art that selective NMDA NR2B antagonists could potentiate the effects of opioids, such as

morphine, thus providing analgesia with suprisingly reduced side-effects, such as motor-impairment. Thus the safety margin for the use of opioids, such as morphine, is surprisingly improved. There is no indication in the art relating to NMDA antagonists that the property of potentiating the action of morphine could be transferred to compounds selective for the NR2B subunit.

As the present specification surprisingly demonstrates that selective NMDA NR2B antagonists possess antinociceptive effects in rat models of inflammatory and neuropathic pain with a much improved side-effect window over non-competitive NMDA antagonists (ataxic/antinociceptive), when combined with an opioid, the combination is better tolerated than expected.

Inhibitors of cyclooxygenase-2 are a sub-class of the class of drugs known as non-steroidal antiinflammatory drugs (NSAIDs). The NSAIDs are active in reducing the prostaglandin-induced pain and swelling associated with the inflammation process but are also active in affecting other prostaglandin-regulated processes not associated with the inflammation process. Thus, use of high doses of most common NSAIDs can produce severe side effects, including life threatenting ulcers, that limit their therapeutic potential. An alternative to NSAIDs is the use of corticosteroids, which have even more drastic side effects, especially when long term therapy is involved.

Previous NSAIDs have been found to prevent the production of prostaglandin by inhibiting enzymes in the human arachidonic acid/prostaglandin pathway including the enzyme cyclooxygenase (COX). The recent discovery that there are two isoforms of the COX enzyme, the first, COX-1, being involved with physiological functions and the second, COX-2, being induced in inflamed tissue, has given rise to a new approach. While conventional NSAIDs block both forms of the enzyme, the identification of the inducible COX-2 enzyme associated with inflammation has provided a viable target of inhibition which more

effectively reduces inflammation and produces fewer and less drastic side effects. Many compounds which have activity as COX-2 inhibitors have been identified, and much research continues in this area.

As the use of COX-2 inhibiting compounds may give rise to side-effects there is a need to develop methods which enable the clinician to use lower doses of them thereby reducing side-effects.

The present invention accordingly provides the use of a selective NMDA NR2B antagonist and a COX-2 inhibitor for the manufacture of a medicament for the treatment or prevention of pain or nociception.

The present invention also provides a method for the treatment or prevention of pain or nociception, which method comprises administration to a patient in need of such treatment an amount of a selective NMDA NR2B antagonist and an amount of a COX-2 inhibitor such that together they give effective pain relief.

In a further aspect of the present invention, there is provided a pharmaceutical composition comprising a selective NMDA NR2B antagonist and a COX-2 inhibitor, together with at least one pharmaceutically acceptable carrier or excipient.

It will be appreciated that the selective NMDA NR2B antagonist and a COX-2 inhibitor may be present as a combined preparation for simultaneous, separate or sequential use for the treatment or prevention of pain. Such combined preparations may be, for example, in the form of a twin pack.

In a further or alternative aspect of the present invention, there is therefore provided a product comprising a selective NMDA NR2B antagonist and a COX-2 inhibitor as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of pain or nociception.

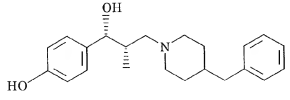
The compositions of the present invention are useful for the treatment of pain of any eitiology, including acute and chronic pain and any pain with an inflammatory component. Examples of acute pain

include, in particular, post-operative pain, migraine, headache and trigeminal neuralgia. Examples of chronic pain include, in particular, pain associated with musculo-skeletal disorders such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, sero-negative (non-rheumatoid) arthropathies, non-articular rheumatism and peri-articular disorders, and pain associated with cancer, peripheral neuropathy and post-herpetic neuralgia. Examples of pain with an inflammatory component (in addition to some of those described above) include rheumatic pain, dental pain and dysmenorrhoea.

The compositions of the present invention are especially useful for the treatment of pain where the use of a COX-2 inhibitor is generally prescribed. By the use of a combination of a selective NMDA NR2B antagonist and an opioid analgesic in accordance with the present invention, it is now possible to treat pain with a sub-maximal dose of an opioid analgesic thereby reducing the likelihood of side-effects associated with opioid analgesic usage (e.g. respiratory depression, constipation, nausea and vomiting, and tolerance and dependence and the associated problem of drug withdrawal).

A particularly preferred use for a composition of the present invention is in the treatment or prevention of post-operative pain.

Selective NMDA NR2B antagonists of use in the present invention include eliprodil (and those of EP-A-109317 and French utility certificate FR 89 04835), ifenprodil (and those of French patent FR 5733 M), Ro25-6981 (and those of EP-A-648744), compounds disclosed in WO-A-9713769 to Pharmacia and CP-101,606 (and those of EP-A-768086). A particularly favoured compound is Ro25-6981:



Particularly suitable selective NMDA NR2B antagonists can be identified by the following cascade which forms a further feature of the present invention. There is accordingly provided an assay for identifying a selective NMDA NR2B antagonist comprising:

(i) determining a compound having an $IC_{50}$ of less than 100 nM affinity at the human NMDA NR2B receptor and having a greater than 100-fold selectivity for NR2B receptors over human $I_{(Kr)}$ cardiac potassium channels in radioligand binding studies;

(ii) demonstrating said compound inhibits hyperalgesia with $ID_{50}$ <30mg/kg i.p. or s.c. and has a greater than 10-fold window between doses producing antinociception and motor disruption in carrageenan-induced hyperalgesia in rats;

(iii) determining said compounds has an $ID_{50}$ of less than 30mg/kg i.p. or s.c. in the rat sciatic nerve ligation assay of neuropathic pain;

(iv) determining said compound has an $ID_{50}$ of less than 30mg/kg p.o. in the rat carrageenan-induced hyperalgesia; and

(vi) demonstrating said compound has synergistic antinociceptive effects in combination with a COX-2 inhibitor in an assay of nociception such as inhibition of hyperalgesia induced by carrageenan or Freund's adjuvant or inhibition of allodynia in neuropathic rats.

The compounds of use in this invention may have one or more asymmetric centres and can therefore exist as enantiomers and possibly as diastereoisomers. It is to be understood that the present invention relates to the use of all such isomers and mixtures thereof.

Suitable pharmaceutically acceptable salts of the selective NMDA NR2B antagonists of use in the present invention include acid addition salts which may, for example, be formed by mixing a solution of the compound with a solution of a pharmaceutically acceptable non-toxic acid such as hydrochloric acid, fumaric acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Salts of amine groups may also comprise the quaternary ammonium salts in which

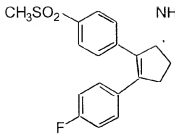
the amino nitrogen atom carries an alkyl, alkenyl, alkynyl or aralkyl group. Where the compound carries an acidic group, for example a carboxylic acid group, the present invention also contemplates salts thereof, preferably non-toxic pharmaceutically acceptable salts thereof, such as the sodium, potassium and calcium salts thereof.

The terms "inhibitor of cyclooxygenase-2", "cyclooxygenase-2 inhibitor" and "COX-2 inhibitor" as used herein embrace compounds which selectively inhibit cyclooxygenase-2 over cyclooxygenase-1. Employing the human whole blood COX-1 assay and the human whole blood COX-2 assay described in C. Brideau et al, Inflamm. Res. *45*: 68-74 (1996), herein incorporated by reference, preferably, the compounds have a cyclooxygenase-2 $IC_{50}$ of less than about 2 mM in the human whole blood COX-2 assay, yet have a cyclooxygenase-1 $IC_{50}$ of greater than about 5 mM in the human whole blood COX-1 assay. Also preferably, the compounds have a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least 10, and more preferably of at least 40. The resulting selectivity may indicate an ability to reduce the incidence of common NSAID-induced side effects.

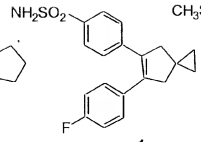
It is particularly preferred that the COX-2 inhibitor be rofecoxib or celecoxib.

As explained in J. Talley, Exp. Opin. Ther. Patents (1997), 7(1), pp. 55-62, three distinct structural classes of selective COX-2 inhibitor compounds have been identified. One class is the methane sulfonanilide class of inhibitors, of which NS-398, flosulide, nimesulide and L-745,337 are example members.

A second class is the tricyclic inhibitor class, which can be further divided into the sub-classes of tricyclic inhibitors with a central carbocyclic ring (examples include SC-57666, **1**, and **2**); those with a central monocyclic heterocyclic ring (examples include DuP 697, SC-58125, SC-58635, and **3**, **4** and **5**); and those with a central bicyclic heterocyclic ring (examples include **6**, **7**, **8**, **9** and **10**). Compounds **3**, **4** and **5** are described in U.S. Patent No. 5,474,995.




SC-57666

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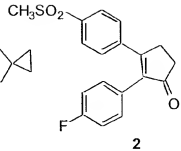


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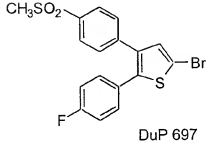
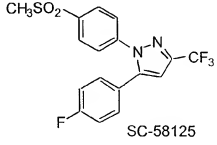



DuP 697

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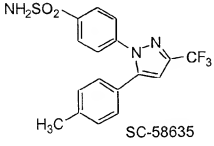


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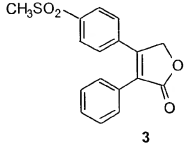


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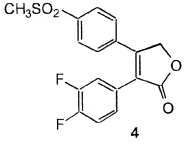


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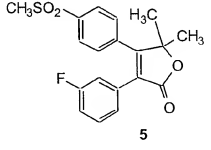


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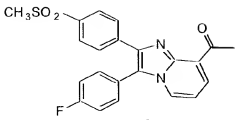


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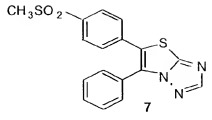


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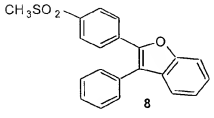


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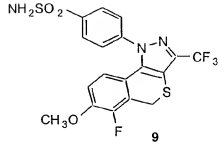


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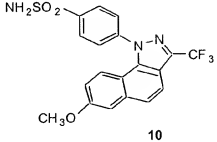


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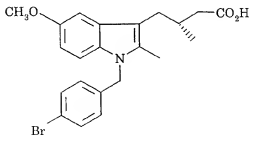
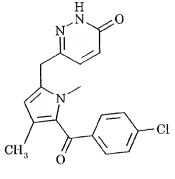
The third identified class can be referred to as those which are structurally modified NSAIDS, and includes L-761,066 and structure 11 as example members.




L-761,066

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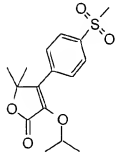
In addition to the structural classes, sub-classes, specific COX-2 inhibitor compound examples, and reference journal and patent publications described in the Talley publication which are all herein incorporated by reference, examples of compounds which selectively inhibit cyclooxygenase-2 have also been described in the following patent publications, all of which are herein incorporated by reference: U.S. Patent No.'s 5,344,991, 5,380,738, 5,393,790, 5,409,944, 5,434,178, 5,436,265, 5,466,823, 5,474,995, 5,510,368, 5,536,752, 5,550,142, 5,552,422, 5,604,253, 5,604,260, 5,639,780; and International Patent Specification Nos. 94/13635, 94/15932, 94/20480, 94/26731, 94/27980, 95/00501, 95/15316, 96/03387, 96/03388, 96/06840; and International Publication No.'s WO 94/20480, WO 96/21667, WO 96/31509, WO 96/36623, WO 97/14691, WO 97/16435.

Additional COX-2 inhibitor compounds which are included in the scope of this invention include:



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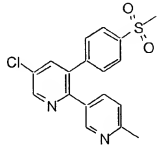

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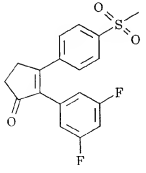

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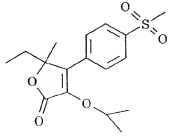

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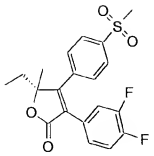

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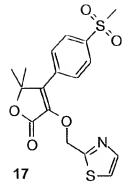

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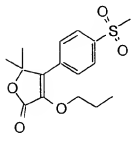

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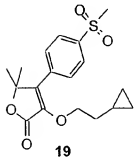

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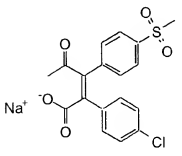

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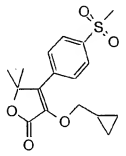

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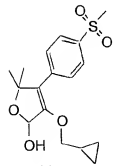

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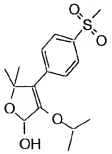

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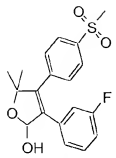

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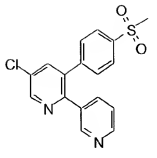

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Some of the compounds above can also be identified by the following chemical names:

**3**: 3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone;

**4**: 3-(3,4-difluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone;

**5**: 5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-3-(3-fluorophenyl)-5H-furan-2-one;

**12**: 5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-3-(2-propoxy)-5H-furan-2-one;

**13**: 5-chloro-3-(4-(methylsulfonyl)phenyl)-2-(2-methyl-5-pyridinyl)pyridine;

**14**: 2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one;

**15**: 5(S)-5-ethyl-5-methyl-4-(4-(methylsulfonyl)phenyl)-3-(2-propoxy)-5H-furan-2-one;

**16**: 5-ethyl-5-methyl-4-(4-(methylsulfonyl)phenyl)-3-(3,4-difluorophenyl)-5H-furan-2-one;

**17**: 3-((2-thiazolyl)methoxy)-4-(4-(methylsulfonyl)phenyl)-5,5-dimethyl-5H-furan-2-one;

**18**: 3-propyloxy-4-(4-(methylsulfonyl)phenyl)-5,5-dimethyl-5H-furan-2-one;

**19**: 3-(1-cyclopropylethoxy)-5,5-dimethyl-4-(4-methylsulfonyl)phenyl)-5H-furan-2-one;

**20**: sodium 2-(4-chlorophenyl)-3-(4-(methylsulfonyl)phenyl)-4-oxo-2-pentenoate;

**21**: 3-(cyclopropylmethoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-5H-furan-2-one;

**22**: 3-(cyclopropylmethoxy)-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-2,5-dihydrofuran-2-ol;

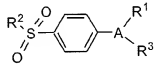
**23**: 3-isopropoxy-5,5-dimethyl-4-(4-(methylsulfonyl)phenyl)-2,5-dihydrofuran-2-ol;

**24**: 5,5-dimethyl-3-(3-fluorophenyl)-2-hydroxy-4-(4-(methylsulfonyl)phenyl)-2,5-dihydrofuran;

**25**: 5-Chloro-3-(4-(methylsulfonyl)phenyl)-2-(3-pyridinyl)pyridine.

The following publications describe and/or provide methods for making the compounds as indicated: compounds 12, 15, 17, 18, 19 and 21, WO 97/14691; compounds 22, 23 and 24, WO 97/16435; compound 20, WO 96/36623; compound 14, U.S. Patent No. 5,536,752; compound 16, U.S. Patent No. 5,474,995. See Examples herein for compounds 13 and 25.

Also incorporated herein by reference are those compounds described in WO 96/41645 as having structural Formula I, shown below, and the definition and preferred definitions and species described therein:



I

Particularly preferred compounds of formula (I) include:

5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole;

4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)pyrazole;

4-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

4-(3,5-bis(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

4-(5-(4-chlorophenyl)-3-phenyl-1H-pyrazol-1-yl)benzenesulfonamide;

4-(3,5-bis(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

4-(5-(4-chlorophenyl)-3-(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

4-(5-(4-chlorophenyl)-3-(4-nitrophenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

4-(5-(4-chlorophenyl)-3-(5-chloro-2-thienyl)-1H-pyrazol-1-yl)benzenesulfonamide;

4-(4-chloro-3,5-diphenyl-1H-pyrazol-1-yl)benzenesulfonamide;

4-(5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide;

4-(5-phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide;

4-(5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide;

4-(5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide;

4-(5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide;

4-(5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide;

4-(4-chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide;

4-(3-(difluoromethyl)-5-(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

4-(3-(difluoromethyl)-5-phenyl-1H-pyrazol-1-yl)benzenesulfonamide;

4-(3-(difluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

4-(3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

4-(3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

4-(5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide;

4-(4-chloro-5-phenyl-1H-pyrazol-1-yl)benzenesulfonamide;

4-(5-(4-chlorophenyl)-3-(hydroxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
4-(5-(4-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide;
5-(4-fluorophenyl)-6-(4-(methylsulfonyl)phenyl)spiro[2.4]hept-5-ene;
4-(6-(4-fluorophenyl)spiro[2.4]hept-5-en-5-yl)benzenesulfonamide;
6-(4-fluorophenyl)-7-(4-(methylsulfonyl)phenyl)spiro[3.4]oct-6-ene;
5-(3-chloro-4-methoxyphenyl)-6-(4-(methylsulfonyl)phenyl)spiro[2.4]hept-5-ene;
4-(6-(3-chloro-4-methoxyphenyl)spiro[2.4]hept-5-en-5-yl)benzenesulfonamide;
5-(3,5-dichloro-4-methoxyphenyl)-6-(4-(methylsulfonyl)phenyl)spiro[2.4]hept-5-ene;
5-(3-chloro-4-fluorophenyl)-6-(4-(methylsulfonyl)phenyl)spiro[2.4]hept-5-ene;
4-(6-(3,4-dichlorophenyl)spiro[2.4]hept-5-en-5-yl)benzenesulfonamide;
2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;
2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;
5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-methylthiazole;
4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;
4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)thiazole;
4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-benzylaminothiazole;
4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(1-propylamino)thiazole;
2-((3,5-dichlorophenoxy)methyl)-4-(4-fluorophenyl)-5-(4-(methylsulfonyl)phenyl)thiazole;
5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;
1-methylsulfonyl-4-(1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl)benzene;
4-(4-(4-fluorophenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl)benzenesulfonamide;

5-(4-fluorophenyl)-6-(4-(methylsulfonyl)phenyl)spiro[2.4]hepta-4,6-diene;
4-(6-(4-fluorophenyl)spiro[2.4]hepta-4,6-dien-5-yl)benzenesulfonamide;
6-(4-fluorophenyl)-2-methoxy-5-(4-(methylsulfonyl)phenyl)-pyridine-3-carbonitrile;
2-bromo-6-(4-fluorophenyl)-5-(4-(methylsulfonyl)phenyl)-pyridine-3-carbonitrile;
6-(4-fluorophenyl)-5-(4-(methylsulfonyl)phenyl)-2-phenyl-pyridine-3-carbonitrile;
4-(2-(4-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl)benzenesulfonamide;
4-(2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl)benzenesulfonamide;
4-(2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl)benzenesulfonamide;
3-(1-(4-(methylsulfonyl)phenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)benzenesulfonamide;
2-(1-(4-(methylsulfonyl)phenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)pyridine;
2-methyl-4-(1-(4-(methylsulfonyl)phenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)pyridine;
2-methyl-6-(1-(4-(methylsulfonyl)phenyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)pyridine;
4-(2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl)benzenesulfonamide;
2-(3,4-difluorophenyl)-1-(4-(methylsulfonyl)phenyl)-4-(trifluoromethyl)-1H-imidazole;
4-(2-(4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl)benzenesulfonamide;
2-(4-chlorophenyl)-1-(4-(methylsulfonyl)phenyl)-4-methyl-1H-imidazole;
2-(4-chlorophenyl)-1-(4-(methylsulfonyl)phenyl)-4-phenyl-1H-imidazole;

2-(4-chlorophenyl)-4-(4-fluorophenyl)-1-(4-(methylsulfonyl)phenyl)-1H-imidazole;

2-(3-fluoro-4-methoxyphenyl)-1-(4-(methylsulfonyl)phenyl)-4-(trifluoromethyl)-1H-imidazole;

1-(4-(methylsulfonyl)phenyl)-2-phenyl-4-trifluoromethyl-1H-imidazole;

2-(4-methylphenyl)-1-(4-(methylsulfonyl)phenyl)-4-trifluoromethyl-1H-imidazole;

4-(2-(3-chloro-4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl)benzenesulfonamide;

2-(3-fluoro-5-methylphenyl)-1-(4-(methylsulfonyl)phenyl)-4-(trifluoromethyl)-1H-imidazole;

4-(2-(3-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl)benzenesulfonamide;

2-(3-methylphenyl)-1-(4-(methylsulfonyl)phenyl)-4-(trifluoromethyl)-1H-imidazole;

4-(2-(3-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl)benzenesulfonamide;

1-(4-(methylsulfonyl)phenyl)-2-(3-chlorophenyl)-4-(trifluoromethyl)-1H-imidazole;

4-(2-(3-chlorophenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl)benzenesulfonamide;

4-(2-phenyl-4-(trifluoromethyl)-1H-imidazol-1-yl)benzenesulfonamide;

4-(2-(4-methoxy-3-chlorophenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl)benzenesulfonamide;

1-allyl-4-(4-fluorophenyl)-3-(4-(methylsulfonyl)phenyl)-5-(trifluoromethyl)-1H-pyrazole;

4-(1-ethyl-4-(4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazol-3-yl)benzenesulfonamide;

N-phenyl-(4-(4-fluorophenyl)-3-(4-(methylsulfonyl)phenyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;

ethyl (4-(4-fluorophenyl)-3-(4-(methylsulfonyl)phenyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)acetate;

4-(4-fluorophenyl)-3-(4-(methylsulfonyl)phenyl)-1-(2-phenylethyl)-1H-pyrazole;

4-(4-fluorophenyl)-3-(4-(methylsulfonyl)phenyl)-1-(2-phenylethyl)-5-(trifluoromethyl)pyrazole;

1-ethyl-4-(4-fluorophenyl)-3-(4-(methylsulfonyl)phenyl)-5-(trifluoromethyl)-1H-pyrazole;

5-(4-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(trifluoromethyl)-1H-imidazole;

4-(4-(methylsulfonyl)phenyl)-5-(2-thiophenyl)-2-(trifluoromethyl)-1H-imidazole;

5-(4-fluorophenyl)-2-methoxy-4-(4-(methylsulfonyl)phenyl)-6-(trifluoromethyl)pyridine;

2-ethoxy-5-(4-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-6-(trifluoromethyl)pyridine;

5-(4-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-2-(2-propynyloxy)-6-(trifluoromethyl)pyridine;

2-bromo-5-(4-fluorophenyl)-4-(4-(methylsulfonyl)phenyl)-6-(trifluoromethyl)pyridine;

4-(2-(3-chloro-4-methoxyphenyl)-4,5-difluorophenyl)benzenesulfonamide;

1-(4-fluorophenyl)-2-(4-(methylsulfonyl)phenyl)benzene;

5-difluoromethyl-4-(4-(methylsulfonyl)phenyl)-3-phenylisoxazole;

4-(3-ethyl-5-phenylisoxazol-4-yl)benzenesulfonamide;

4-(5-difluoromethyl-3-phenylisoxazol-4-yl)benzenesulfonamide;

4-(5-hydroxymethyl-3-phenylisoxazol-4-yl)benzenesulfonamide;

4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide;

1-(2-(4-fluorophenyl)cyclopenten-1-yl)-4-(methylsulfonyl)benzene;

1-(2-(4-fluoro-2-methylphenyl)cyclopenten-1-yl)-4-(methylsulfonyl)benzene;

1-(2-(4-chlorophenyl)cyclopenten-1-yl)-4-(methylsulfonyl)benzene;

1-(2-(2,4-dichlorophenyl)cyclopenten-1-yl)-4-(methylsulfonyl)benzene;

1-(2-(4-trifluoromethylphenyl)cyclopenten-1-yl)-4-(methylsulfonyl)benzene;
1-(2-(4-methylthiophenyl)cyclopenten-1-yl)-4-(methylsulfonyl)benzene;
1-(2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl)-4-(methylsulfonyl)benzene;
4-(2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl)benzenesulfonamide;
1-(2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl)-4-(methylsulfonyl)benzene;
4-(2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl)benzenesulfonamide;
4-(2-(4-fluorophenyl)cyclopenten-1-yl)benzenesulfonamide;
4-(2-(4-chlorophenyl)cyclopenten-1-yl)benzenesulfonamide;
1-(2-(4-methoxyphenyl)cyclopenten-1-yl)-4-(methylsulfonyl)benzene;
1-(2-(2,3-difluorophenyl)cyclopenten-1-yl)-4-(methylsulfonyl)benzene;
4-(2-(3-fluoro-4-methoxyphenyl)cyclopenten-1-yl)benzenesulfonamide;
1-(2-(3-chloro-4-methoxyphenyl)cyclopenten-1-yl)-4-(methylsulfonyl)benzene;
4-(2-(3-chloro-4-fluorophenyl)cyclopenten-1-yl)benzenesulfonamide;
4-(2-(2-methylpyridin-5-yl)cyclopenten-1-yl)benzenesulfonamide;
ethyl 2-(4-(4-fluorophenyl)-5-(4-(methylsulfonyl)phenyl)oxazol-2-yl)-2-benzyl-acetate;
2-(4-(4-fluorophenyl)-5-(4-(methylsulfonyl)phenyl)oxazol-2-yl)acetic acid;
2-(tert-butyl)-4-(4-fluorophenyl)-5-(4-(methylsulfonyl)phenyl)oxazole;
4-(4-fluorophenyl)-5-(4-(methylsulfonyl)phenyl)-2-phenyloxazole;
4-(4-fluorophenyl)-2-methyl-5-(4-(methylsulfonyl)phenyl)oxazole; and
4-(5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl)benzenesulfonamide;
or a pharmaceutically acceptable salt thereof.

The compounds of use in this invention may have one or more chiral centers and the present compounds may occur as racemates, racemic mixtures and as individual diasteriomers or enantiomers with all such isomeric forms and mixtures thereof being included within the scope of this invention. Furthermore, some of the crystalline forms for compounds

of the present invention may exist as polymorphs and as such are intended to be included in the present invention. In addition, some of the compounds of the instant invention may form solvates with water or common organic solvents. Such solvates and hydrates, as well as anhydrous compositions, are encompassed within the scope of this invention. Some of the compounds described herein may contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

The COX-2 inhibitors that may be used with this invention encompass all pharmaceutically acceptable salt forms of the compounds. Examples of such salt forms of COX-2 inhibitors include but are not limited to salts derived from inorganic bases including aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

As stated above, the selective NMDA NR2B antagonist and COX-2 inhibitor may be formulated in a single pharmaceutical composition or alternatively in individual pharmaceutical compositions for simultaneous, separate or sequential use in accordance with the present invention.

Preferably the compositions according to the present invention are in unit dosage forms such as tablets, pills, capsules, powders, granules, solutions or suspensions, or suppositories, for oral, parenteral or rectal administration, or administration by inhalation or insufflation.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil

suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

Preferred compositions for administration by injection include those comprising a selective NMDA NR2B antagonist, as the active ingredient, in association with a surface-active agent (or wetting agent or surfactant) or in the form of an emulsion (as a water-in-oil or oil-in-water emulsion).

Suitable surface-active agents include, in particular, non-ionic agents, such as polyoxyethylenesorbitans (e.g. Tween™ 20, 40, 60, 80 or 85) and other sorbitans (e.g. Span™ 20, 40, 60, 80 or 85). Compositions with a surface-active agent will conveniently comprise between 0.05 and 5% surface-active agent, and preferably between 0.1 and 2.5%. It will be appreciated that other ingredients may be added, for example mannitol or other pharmaceutically acceptable vehicles, if necessary.

Suitable emulsions may be prepared using commercially available fat emulsions, such as Intralipid™, Liposyn™, Infonutrol™, Lipofundin™ and Lipiphysan™. The active ingredient may be either dissolved in a pre-mixed emulsion composition or alternatively it may be dissolved in an oil (e.g. soybean oil, safflower oil, cottonseed oil, sesame oil, corn oil or almond oil) and an emulsion formed upon mixing with a phospholipid (e.g. egg phospholipids, soybean phospholipids or soybean lecithin) and water. It will be appreciated that other ingredients may be added, for example gylcerol or glucose, to adjust the tonicity of the emulsion. Suitable emulsions will typically contain up to 20% oil, for example, between 5 and 20%. The fat emulsion will preferably comprise fat droplets between 0.1 and 1.0μm, particularly 0.1 and 0.5μm, and have a pH in the range of 5.5 to 8.0.

Particularly preferred emulsion compositions are those prepared by mixing a selective NMDA NR2B antagonist with Intralipid™ or the components thereof (soybean oil, egg phospholipids, glycerol and water).

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulised by use of inert gases. Nebulised solutions may be breathed directly from the nebulising device or the nebulising device may be attached to a face mask, tent or intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

The present invention futher provides a process for the preparation of a pharmaceutical composition comprising a selective NMDA NR2B antagonist and a COX-2 inhibitor, which process comprises bringing a selective NMDA NR2B antagonist and a COX-2 inhibitor into association with a pharmaceutically acceptable carrier or excipient.

When administered in combination, either as a single or as separate pharmaceutical composition(s), the selective NMDA NR2B antagonist and the COX-2 inhibitor are presented in a ratio which is consistent with the manifestation of the desired effect. In particular, the ratio by weight of the selective NMDA NR2B antagonist to the COX-2 inhibitor will suitably be approximately 1 to 1. Preferably this ratio will be between 0.001 to 1 and 1000 to 1, and especially between 0.01 to 1 and 100 to 1.

A suitable dosage level for the selective NMDA NR2B antagonist is about 0.001 to 25mg/kg per day, preferably about 0.005 to 10mg/kg per day, and especially about 0.005 to 5mg/kg per day. The compounds may

be administered on a regimen of up to 6 times per day, preferably 1 to 4 times per day.

The COX-2 inhibitor may be administered at a dosage level up to conventional dosage levels for such analgesics, but preferably at a reduced level in accordance with the present invention. Suitable dosage levels will depend upon the analgesic effect of the chosen COX-2 inhibitor, but typically suitable levels will be about 0.001 to 25mg/kg per day, preferably 0.005 to 10mg/kg per day, and especially 0.005 to 5mg/kg per day. The compound may be administered on a regimen of up to 6 times per day, preferably 1 to 4 times per day.

It will be appreciated that the amount of a selective NMDA NR2B antagonist and COX-2 inhibitor required for use in the treatment or prevention of pain or nociception will vary not only with the particular compounds or compositions selected but also with the route of administration, the nature of the condition being treated, and the age and condition of the patient, and will ultimately be at the discretion of the attendant physician.

The following examples illustrate pharmaceutical compositions according to the invention.

These formulations may be prepared with separate active ingredients or with with a combination of active ingredients in one composition. In such combined preparations, the ratio of selective NMDA NR2B antagonist to COX-2 inhibitor will depend upon the choice of active ingredients.

EXAMPLE 1A Tablets containing 1-25mg of compound

| | Amount mg | | |
|---|---|---|---|
| Active Ingredients(s) | 1.0 | 2.0 | 25.0 |
| Microcrystalline cellulose | 20.0 | 20.0 | 20.0 |
| Modified food corn starch | 20.0 | 20.0 | 20.0 |
| Lactose | 58.5 | 57.5 | 34.5 |
| Magnesium Stearate | 0.5 | 0.5 | 0.5 |

EXAMPLE 1B Tablets containing 26-100mg of compound

| | Amount mg | | |
|---|---|---|---|
| Active Ingredients(s) | 26.0 | 50.0 | 100.0 |
| Microcrystalline cellulose | 80.0 | 80.0 | 80.0 |
| Modified food corn starch | 80.0 | 80.0 | 80.0 |
| Lactose | 213.5 | 189.5 | 139.5 |
| Magnesium Stearate | 0.5 | 0.5 | 0.5 |

The active ingredient(s) cellulose, lactose and a portion of the corn starch are mixed and granulated with 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets containing 1.0mg, 2.0mg, 25.0mg, 26.0mg, 50.0mg and 100mg of the active compound per tablet.

EXAMPLE 2 Parenteral injection

| | Amount |
|---|---|
| Active Ingredient(s) | 1 to 100mg |
| Citric Acid Monohydrate | 0.75mg |
| Sodium Phosphate | 4.5mg |
| Sodium Chloride | 9mg |
| Water for injection | to 10ml |

The sodium phosphate, citric acid monohydrate and sodium chloride are dissolved in a portion of the water. The active ingredient(s) is (are) dissolved or suspended in the solution and made up to volume.

EXAMPLE 3 Topical formulation

| | Amount |
|---|---|
| Active Ingredient(s) | 1-10g |
| Emulsifying Wax | 30g |
| Liquid paraffin | 20g |
| White Soft Paraffin | to 100g |

The white soft paraffin is heated until molten. The liquid paraffin and emulsifying wax are incorporated and stirred until dissolved. The active ingredient(s) is (are) is added and stirring continued until dispersed. The mixture is then cooled until solid.

Example 4A - (Surface-Active Agent) Injection Formulation

| | |
|---|---|
| Active Ingredient(s) | up to 10mg/kg |
| Tween 80™ | up to 2.5% |
| [in 5% aqueous mannitol (isotonic)] | |

The active ingredient(s) is (are) dissolved directly in a solution of the commercially available Tween 80™ (polyoxyethylenesorbitan monooleate) and 5% aqueous mannitol (isotonic).

Example 4B - (Emulsion) Injection Formulation

| | |
|---|---|
| Active Ingredient(s) | up to 30mg/ml |
| Intralipid™ (10-20%) | |

The active ingredient(s) is (are) dissolved directly in the commercially available Intralipid™ (10 or 20%) to form an emulsion.

Example 4C - Alternative (Emulsion) Injectable Formulation

| | Amount |
|---|---|
| Active Ingredient(s) | 0.1 - 10mg |
| Soybean oil | 100mg |
| Egg Phospholipid | 6mg |
| Glycerol | 22mg |
| Water for injection | to 1ml |

All materials are sterilized and pyrogen free. The active ingredient(s) is (are) dissolved in soybean oil. An emulsion is then formed by mixing this solution with the egg phospholipid, glycerol and water. The emulsion is then sealed in sterile vials.

The following Example illustrates that selective NMDA NR2B receptor antagonists have a reduced motor side-effect profile when compared with NMDA/glycine antagonists.

EXAMPLE 5

The present Example examined whether NMDA NR2B receptor antagonists have an improved therapeutic window over unselective NMDA/glycine antagonists and other ion channel blockers including lamotrigine and gabapentin, by comparing their anti-algesic effects with their liability to induce motor impairment in rats. Anti-algesic activity was assessed using an assay of neuropathic pain in rats (sciatic nerve ligation) and in a carrageenan-induced hyperalgesia assay. Motor impairment was measured using an accelerating rotarod.

Methods

For sciatic nerve ligation, male Sprague Dawley rats (180-220g) were anaesthetised with isofluorane, the left sciatic nerve exposed and 4 chromic catgut (4.0) ligatures were tied loosely around the nerve (spaced 1-2 mm apart) immediately proximal to the point of trifurcation. In sham-operated animals, the same dissection was performed but without ligation. Responses to mechanical pressure were assessed 7 days after ligation using a modified Randall-Selitto algesiometer in which constant force of 40 mmHg was applied to the hind paw and the latency to struggle was recorded as the reaction time. Mechanical allodynia was defined as the difference in reaction time for sham and ligature rats. Reaction times for drug treated rats were expressed as a percentage of this response. Compounds were administered 1 h before the test.

In the carrageenan-induced hyperalgesia assay, male Sprague Dawley rats (100-120 g) received an intraplantar injection of carrageenan (4.5 mg) and mechanical thresholds were determined 3 h later using a modified Ugo Basile Algesiometer. Control rats received saline (0.15 ml i.pl.). Hyperalgesia was defined as the difference in vocalisation threshold for saline- and carrageenan-injected rats. Paw pressure scores for drug-treated rats were expressed as a percentage of this response. Compounds were administered 2 h after carrageenan.

To determine the effects of the compounds on motor co-ordination, male Sprague Dawley rats (160-180 g) were first trained to remain for 120 s on the rotarod apparatus revolving at 12 r.p.m. on the morning before the test. Animals then received drug treatments and 1 h later were placed on an accelerating rotarod (increasing from 4 - 40 r.p.m. during a 5 min period) and the time the rats were able to remain on the rotarod recorded. Lamotrigine, gabapentin and (±)-CP-101,606 were suspended in 0.5% methocel and administered orally (1 ml/kg). Ifenprodil, L-701,324, L-687,414 and (±)-Ro25-6981 were dissolved or suspended in in 0.5% methocel and administered intraperitoneally (1 ml/kg). MK-801 was

dissolved in distilled water and given i.p. (1 ml/kg). Doses of compounds refer to the free base.

**Results**

*Anti-algesia studies*

Animals with sciatic nerve ligation exhibited mechanical allodynia as measured by the reduction in the reaction time to withdraw the injured limb from the paw pressure apparatus Reaction times for sham and ligature rats were typically 22 ± 1 s and 8 ± 1 s, respectively. The NMDA NR2B antagonists, (±)-CP-101,606 and (±)-Ro25-6981, the NMDA/glycine receptor antagonist L-701,324 and partial agonist L-687,414 and the non-competitive NMDA antagonist MK-801 dose-dependently reversed mechanical allodynia induced by sciatic nerve ligation (Table 1). Similarly, the novel anti-convulsant drugs, lamotrigine and gabapentin, and the vasodilator ifenprodil, which has affinity for the NMDA NR2B receptor, reversed mechanical allodynia. The order of potency was: MK-801 > L-701,324 > (±)-Ro25-6981 > (±)-CP-101,606 > ifenprodil > L-687,414 > lamotrigine > gabapentin.

Intraplantar injection of carrageenan (4.5 mg) induced marked paw oedema and hyperalgesia to mechanical compression of the inflamed hind paw. All the compounds caused a dose-dependent inhibition of mechnical hyperalgesia induced by carrageenan (Table 1). The order of potency was: MK-801 > L-701,324 > (±)-Ro25-6981 > ifenprodil > (±)-CP-101,606 > L-687,414 = gabapentin > lamotrigine.

*Effects on behaviour and motor co-ordination*

Vehicle-treated rats were able to remain on the accelerating rotarod for approximately 140 s. MK-801 dose-dependently induced impairments in rotarod performance with an $ID_{50}$ of 0.22 mg/kg i.p. Body rolling, and head weaving were also observed following 0.3 and 1 mg/kg doses of MK-801. The NMDA/glycine receptor antagonist L-701,324 and partial agonist

L-687,414 also induced rotarod deficits ($ID_{50}$ of 1.9 mg/kg i.p. and 53.3 mg/kg i.p.); ataxia was evident at 10 and 30 mg/kg i.p. of L-701,324 and L-687,414 induced body rolling and ataxia at 100 and 300 mg/kg i.p. Ifenprodil caused approximately 50% impairment in rotarod performance at 50 mg/kg, however, severe adverse effects were also observed at this dose (ptosis, pilorecetion, hypoactivity and hyperventilation). Gabapentin caused motor impairments (ataxia) at doses of 30-300 mg/kg ($ID_{50}$ for rotarod was 133 mg/kg i.p.). Administration of lamotrigine at 500 mg/kg p.o. caused a 40% inhibition in the time spent on the rotarod; no other effects were observed at this dose. Similarly, (±)-Ro25-6981 induced a 47% inhibition of rotarod performance at a dose of 100 mg/kg i.p. (±)-CP-101,606 did not inhibit motor performace on the rotarod up to 300 mg/kg p.o.; in fact, there was a significant increase in latency following 300 mg/kg dose compared to vehicle-treated rats.

The mean ratios for the $ID_{50}$ inducing motor impairment and inhibition of allodynia in neuropathic rats were at least 4 fold greater for the NMDA NR2B receptor antagonists, (±)-CP-101,606 (ratio >49) and (±)-Ro25-6981 (ratio ≥26), than were found for MK-801 (ratio 1.1), the NMDA/glycine antagonists (ratio <6), gabapentin (ratio 1.5) and ifenprodil (ratio 5.3). Lamotrigine had a similar profile to that of the NMDA NR2B receptor antagonists (ratio >45).

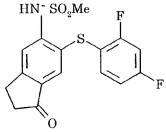
**Conclusions**

These data suggest that NMDA NR2B antagonists may be useful for treating neuropathic pain in man with an improved therapeutic window over clinically used unselective ion channel blockers.

Table 1. Summary of the anti-algesic and ataxic properties of NMDA receptor antagonists and other ion channel blockers

| | $ID_{50}$ (mg/kg) | | | |
|---|---|---|---|---|
| | Antinociception | | Motor Impairment | Ratio |
| | Rat Ligation | Rat Carrageenan | Rat Rotarod | Rotarod/ Rat Ligation |
| Lamotrigine (p.o.) | 11 | 207 | >500 | >45 |
| Gabapentin (p.o.) | 87 | 50 | 133 | 1.5 |
| Ifenprodil (i.p.) | 9.5 | 17 | ≥50 | 5.3 |
| MK-801 (i.p.) | 0.19 | 0.21 | 0.22 | 1.1 |
| L-701,324 (i.p.) | 2.6 | 2.5 | 1.9 | 0.7 |
| L-687,414 (i.p.) | 9.8 | 50 | 53 | 5.4 |
| CP-101,606 (p.o.) | 6.1 | 37 | >300 | >49 |
| RO25-6981 (i.p.) | 3.8 | 5.7 | ≥100 | ≥26 |

The following Example demonstrates the synergistic antinociceptive effects of a combined treatment of the selective NMDA NR2B antagonist (±)-Ro25-6981 with the COX-2 inhibitor L-745,337:




L-745,337

EXAMPLE 6

The present Example examined whether the NMDA NR2B antagonist (±)-Ro25-6981 could potentiate the antinociceptive effects of a COX-2 inhibitor, L-745,337, in an assay of inflammatory hyperalgesia in rats to determine whether such combination therapies may provide improved analgesic efficacy in man with reduced side-effects.

**Methods**

Male Sprague Dawley rats (100-120 g) received an intraplantar injection of carrageenan (4.5 mg) and mechanical thresholds were determined 3 h later using a modified Ugo Basile Algesiometer. Control rats received saline (0.15 ml i.pl.). Hyperalgesia was defined as the difference in vocalisation threshold for saline- and carrageenan-injected rats. Paw pressure scores for drug-treated rats were expressed as a percentage of this response. Compounds were administered 2 h after carrageenan.

To determine the effects of morphine and (±)-Ro25-6981 on motor co-ordination, male Sprague Dawley rats (160-180 g) were first trained to remain for 120 s on the rotarod apparatus revolving at 12 r.p.m. on the morning before the test. Animals then received drug treatments and 1 h

later were placed on an accelerating rotarod (increasing from 4 - 40 r.p.m. during a 5 min period) and the time the rats were able to remain on the rotarod recorded.

(±)-Ro25-6981 was suspended in 0.5% methocel and administered intraperitoneally (1 ml/kg). L-745,337 was suspended in 0.5% methocel and given orally (2 ml/kg). Doses of compounds refer to the free base.

**Results**

Effect of (±)-Ro25-6981 on Carrageenan-Induced Hyperalgesia

Intraplantar injection of carrageenan (4.5 mg) induced marked paw oedema and hyperalgesia to mechanical compression of the inflamed hind paw. Intraperitoneal (i.p.) administration (±)-Ro25-6981 caused a dose-dependent reversal of mechanical hyperalgesia induced by carrageenan at doses of 10 and 30 mg/kg (Figure 1). A dose of 1 mg/kg was chosen for combination experiments as this did not cause significant antinociception.

Combination of (±)-Ro25-6981 and COX-2 inhibitor L-745,337

Oral (p.o.) administration of L-745,337 (0.3-3 mg/kg) alone caused a dose-dependent inhibition of hyperalgesia which was significant at the 3 mg/kg dose alone (75% inhibition) (Figure 2). Combined treatment with (±)-Ro25-6981 (1 mg/kg i.p.) and L-745,337 (0.3-3 mg/kg) again resulted in a greater inhibition of hyperalgesia (Figure 2).

**Conclusions**

These data demonstrate that administration of (±)-Ro25-6981, at a dose that is ineffective by itself, can markedly potentiate the antinociceptive effects of L-745,337. These findings suggest that NMDA NR2B receptor antagonists may be useful as combination therapy with NSAIDs to increase analgesic efficacy and reduce the incidence of side effects in man by enabling a reduction in the dose of these agents.

## CLAIMS

1. A product comprising a selective NMDA NR2B antagonist and a COX-2 inhibitor as a combined preparation for simultaneous, separate or sequential use in the treatment on prevention of pain or nociception.

2. A product according to claim 1 wherein the NR2B antagonist is eliprodil or ifenprodil.

3. A product recording to claim 1 or 2 wherein the COX-2 inhibitor is celeboxib, or rofecoxib

4. A pharmaceutical composition comprising a selective NMDA NR2B antagonist and a COX-2 inhibitor; together with at least one pharmaceutically acceptable carrier or excipient.

5. The use of a selective NMDA NR2B antagonist and a COX-2 inhibitor for the manufacture of a medicament for the treatment of pain or nociception.

6. A method for the treatment or prevention of pain or nociception, which method comprises administration to a patient in need of such treatment an amount of a selective NMDA NR2B antagonist and an amount of a COX-2 inhibitor such that together they give effective pain relief.

7. A process for the preparation of a pharmaceutical composition comprising a selective NMDA NR2B antagonist and a COX-2 inhibitor, which process comprises bringing a selective NMDA NR2B antagonist and a COX-2

inhibitor into association with a pharmaceutially acceptable carrier or excipient.

Figure 1

**Inhibition of carrageenan-induced mechanical hyperalgesia by the NMDA NR2B antagonist R025-6981 in rats**

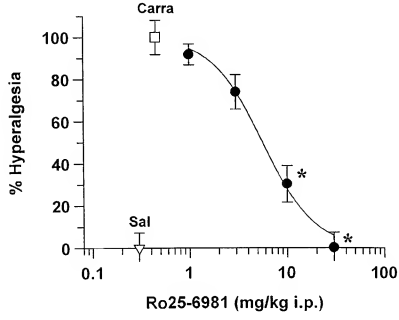
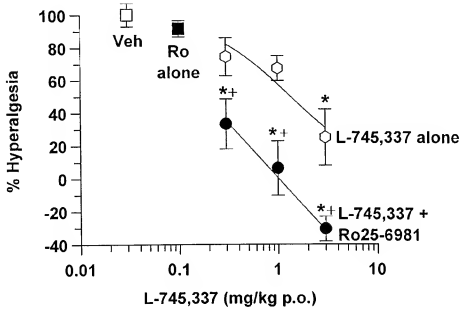


Figure 2

**Effect of combination of the cox-2 inhibitor L-745,337 and the NMDA NR2B antagonist Ro25-6981 on carrageenan-induced hyperalgesia**




(Ro25-6981 1 mg/kg i.p.)

* $p < 0.05$ compared to vehicle treated

\+ $p < 0.05$ compared to L-745,337 alone

# INTERNATIONAL SEARCH REPORT

Int ational Application No
PCT/GB 99/00581

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K45/06 A61K31/445 //(A61K31/445,31:34),(A61K31/445,31:18)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | US 5 409 944 A (BLACK W CAMERON ET AL) 25 April 1995 (1995-04-25) column 5, line 55 - column 7, line 42; claim 18 --- | 1-7 |
| A | US 5 521 213 A (PRASIT PETPIBOON ET AL) 28 May 1996 (1996-05-28) column 5, line 36 - column 6, line 65 --- | 1-7 |
| A | WO 96 19469 A (MERCK FROSST CANADA INC ;BLACK CAMERON (CA); GRIMM ERICH (CA); LEG) 27 June 1996 (1996-06-27) page 22, line 33 - page 23, line 18 ----- | 1-7 |

☐ Further documents are listed in the continuation of box C

☒ Patent family members are listed in annex.

* Special categories of cited documents

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 27 July 1999 | 04/08/1999 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016 | Leherte, C |

Form PCT/ISA/210 (second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/00581

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons.

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims relate to an extremely large number of possible combinations. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the combinations claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the combinations mentionned in the examples of the description.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Int tional Application No
PCT/GB 99/00581

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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| | | CA 2157107 A | 14-09-1994 |
| | | WO 9420480 A | 15-09-1994 |
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| | | JP 10511089 T | 27-10-1998 |